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Symptoms of estrogen deprivation commonly occur in breast cancer survivors as a result of natural menopause, or menopause that is precipitated prematurely by chemotherapy or anti-estrogen therapy with tamoxifen. In this research program we are evaluating the role of a comprehensive menopausal assessment (CMA) and intervention program for management of menopausal symptoms in breast cancer survivors. During the past funding year we have recruited and trained our research staff, developed the intervention and outcome assessment procedures, and pilot-tested the intervention in 9 subjects. We are about to initiate the randomized trial in which we will assign symptomatic postmenopausal breast cancer survivors to an experimental or usual-care group. The experimental group will receive immediate assessment and intervention for their symptoms while the control group will receive no menopause related intervention during a four month period of observation. Systematic assessment of each breast cancer survivor assigned to the intervention will permit treatment of multiple symptoms simultaneously with a variety of non-estrogen pharmacologic, educational and behavioral interventions. We will be assessing the impact of the intervention on quality of life and the resolution of specific menopausal symptoms.

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FOREWORD

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Patricia Garza 10/10/96

PI - Signature Date

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Introduction

Breast cancer is the leading cause of cancer in women, affecting 1 in 9 women in the U.S. According to the most recent SEER data, women with breast cancer have a relative 5-year survival rate of over 75%. Earlier detection of breast cancer, as well as improvements in post-operative adjuvant therapies, have enhanced the long term survival for women with this diagnosis. Symptoms of estrogen deprivation commonly occur in breast cancer survivors as a result of natural menopause, or menopause that is precipitated prematurely by chemotherapy or anti-estrogen therapy with tamoxifen. Hormone replacement therapy, the most efficacious treatment for these symptoms, is generally contraindicated in breast cancer survivors because of its potential risk of inducing a recurrence of breast cancer. Thus, many breast cancer survivors endure considerable morbidity and impaired quality of life (QL) as a result.

This research program will evaluate the role of a comprehensive menopausal assessment (CMA) and intervention program for management of menopausal symptoms in breast cancer survivors. Using a randomized controlled design, we will assign symptomatic postmenopausal breast cancer survivors to an experimental or usual-care group. The experimental group will receive immediate assessment and intervention for their symptoms while the control group will receive no menopause related intervention during a four month period of observation. Systematic assessment of each breast cancer survivor assigned to the intervention will permit treatment of multiple symptoms simultaneously with a variety of non-hormonal pharmacologic, educational and behavioral interventions. The intervention program will be portable, and suitable for implementation in a variety of health care settings. We will evaluate the impact of the intervention on QL and the resolution of specific menopausal symptoms. QL will be assessed using standardized measures of health status, mood, and sexual functioning. Menopausal symptoms will be monitored using self-report diary cards. Our primary hypothesis is that the intervention program will lead to significant improvement in QL for breast cancer survivors.

Progress report on second year of funding

Recruitment and Subject Characteristics

During the past year, we completed a pilot study in 6 subjects and began the randomized trial as of January 31, 1996. As of October 1, 1996, a total of 88 women have been screened over the telephone for the randomized trial. Of those, 51 (58%) were eligible and interested in participating in the study. The current status of these 51 women is as follows:

11 have completed the study
- 6 in the experimental group
- 5 in the usual care group

29 are currently in the study

2 are on hold
4 have dropped out voluntarily
5 were removed from the study
    2 had their target symptoms disappear between the screener and the baseline visit
    2 were non-compliant to their first appointment
    1 refused to take study medications

The attached Tracking Flow Chart (on page 9) gives more detail about how many women have completed each phase of the study. Subject recruitment has been a more significant problem than expected and we have implemented additional activities to enhance recruitment (see below).

Women were found ineligible for four main reasons: Inadequate target symptoms (44%), Medical ineligibility (28%), Refusal to try our study medications (22%) and Already tried all our study medications (6%). The 36 ineligible women look similar to the 51 eligible women. Below are some demographic statistics from the two groups.

	Eligible (N=51)	Not Eligible (N=37)
Mean Age	51.6	54.2
% White	90.4%	89.9%
% Married	65.4%	63.9%
% Currently Taking Tamoxifen	48.1%	54.3%

Because recruitment was lower and ineligibility was higher than anticipated, we have developed additional strategies for subject recruitment. We recently put an advertisement for the study in the Los Angeles Times, and the response has been very good. We have also distributed announcements about the study at health fairs and through breast cancer support groups. We also anticipate having a feature story in the Los Angeles Times describing our research on the menopause and breast cancer. We plan to continue to pursue all of these approaches to ensure completion of target accrual for the study.

Target Symptoms in Study Subjects

The three target symptoms under evaluation in this study are hot flashes, vaginal dryness and urinary incontinence. Among women entering the study, 89% reported severe hot flashes, 39% reported vaginal dryness and only 8% reported stress incontinence. Thirty three percent of entering women reported two or more of these symptoms. During the study, women report the frequency and severity of their target symptoms on baseline and follow-up questionnaires and also on diary cards, which they fill out on a daily basis for the four weeks preceding their baseline and their follow-up visits. Change in symptoms over time will be described in the two study groups.

Refinement of Outcome Variables

The goal of this study is to see if the targeted intervention, the CMA (Comprehensive Menopause Assessment) will improve quality of life for breast cancer survivors who are experiencing at least one severe menopausal symptom. Review of pilot data for this study suggested that the QL measure with the most significant abnormality in this population is the MOS role limitations/emotional scale. This scale is an SF-36 scale which measures how much a person's role function is affected by emotional limitations. It measures an aspect of quality of life which applies to everyone in the study, and it is an area which is likely to improve through the CMA.

Other exploratory analyses from the questionnaire data and the symptom diary card data are planned, e.g. predictors of role function limitations/emotional and the reliability of the diary card data as compared to the symptom checklist in the questionnaire booklet.

Sample Size Considerations

The original sample size was computed before any specific data were collected in the study target population. In August 1996, the sample size was reexamined using data from the current study sample. For this analysis, we used baseline data on 22 women, 3 of whom were pilot subjects and were not included in the randomized trial.

In this study, we will compare women who have received the CMA (experimental group) with women who have not (usual care group). For the primary outcome variable, role function limitations/emotional, the study sample had a mean of 69.7 and a standard deviation of 36.7 at baseline. This score is considerably lower than a reference sample of breast cancer survivors taken from the UCLA Georgetown Women's Health Study, who have a mean of 78.2 and a standard deviation of 34.7. However, the reference sample of breast cancer survivors includes some depressed women and this study excludes subjects who are depressed. Through the CMA, we expect to be able to achieve an increase in role function/emotional score to a mean score in the experimental group of 82 (which is approximately 1/3 of a standard deviation increase). Therefore, using role function/emotional as the outcome variable and setting a significance level of α=.05 and a power of 80%, we estimate the following sample sizes:

1-sided test: 113 women in each group
2-sided test: 143 women in each group

It is unlikely that the women in the experimental group, who will be receiving the extra personal attention of the CMA along with study medications to help alleviate their symptoms, will worsen between baseline and follow-up. Therefore we could reasonably expect the mean for the experimental group to go up between baseline and completion of the study 4 months later. Therefore, we believe a 1-sided test would be sufficient with a total of 226 women, half in the control group and half in the intervention group.

Conclusion

During the past year the randomized trial was begun and subjects have participated in this process, which includes longitudinal follow-up and data collection. A total of 40 subjects are currently in the process on study, or have completed the study. Clearly, recruitment thus far has been slower than expected, with ineligibility primarily due to insufficient severity of symptoms and/or unwillingness to try a study medication. Our recent recruitment efforts through advertising have been encouraging, and we will continue our efforts to publicize the study and recruit eligible subjects. Although the original research plan called for completion of recruitment in the third year of the study, we may need to extend recruitment into the fourth year of the research.

UCLA Menopause Study Tracking Flow Chart As of October 1, 1996